Original Article

Efficacy and Safety of 28 days Treatment with Sodium Phosphate Solution in Management of Chronic Constipation (Preliminary Study)

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ABSTRACT

Background: Nowadays the treatment of chronic constipation has been far from satisfaction. Sodium Phosphate (NaP) solution has been used for a long time as effective colorectal cleansing. This study aims to define dosing of NaP solution in patient with chronic constipation.

Patients and Methods: According to ROME III criteria, adult ambulatory patients with chronic constipation were included. Enrolled subjects were randomly assigned to treatment with NaP solution 10 or 20 cc. daily for 28 days. Patients recorded their bowel movements and associated symptoms on daily basis. Vital signs and blood chemistry were assessed weekly.

Results: Seventeen patients were enrolled. Eight patients were assigned to receive 10 cc. NaP solution (group 1) and 9 patients to 20 cc. NaP solution (group 2). Treatment success was ranging from 50% to 71% in group 1 and 100% in group 2. No patient in group 1 but 8 of 9 patients in group 2 developed watery stool. No patient had serious adverse event in both groups. Two patients in group 2 developed mild hypokalemia and hypocalcemia. Meanwhile, in treatment group, no one had postural hypotension, renal insufficiency or hypophosphatemia.

Conclusion: NaP solution 20 cc. was effective to increase bowel movement with evidence of watery stool in most cases. NaP solution 10 cc. seemed reasonable for further study about its efficacy and safety for a constipation patient.

Key words : sodium phosphate, constipation

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INTRODUCTION

Constipation is a common problem, with an estimated prevalence of 2-28%.[1] The prevalence of chronic constipation from Thai Motility Club study is about 23.5%. In United States, chronic constipation results in more than 2.5 million physician visits annually, 92,000 hospitalizations and several hundred million dollars of laxative sales per year.[1] Moreover, constipation was also associated with impaired quality of life.[1] Although it is a common problem, the treatment of chronic constipation has been far from satisfaction. There is a need for additional treatments, particularly for those with severe constipation.

Sodium Phosphate (NaP) has two oral forms, solution and tablets. NaP solution is an osmotic laxative that has been available in the United States as an over-the-counter product for more than 100 years. Its efficacy and tolerability was generally similar to or significantly better than, that of polyethylene glycol (PEG) or other colorectal cleansing regimens in patients preparing for colonoscopy, colorectal surgery or other colorectal-related procedures.[2] NaP-associated adverse events were mostly gastrointestinal complaints (including abdominal pain/cramping, abdominal fullness and/or bloating, anal or perianal irritation or soreness, nausea, vomiting and hunger pains).

A search of MEDLINE found only one published clinical study on the use of NaP tablets 4 weeks for the treatment of constipation.[3] From this small study, taking NaP tablets daily were generally well tolerated, produced prompt relief of constipation that was sustained over the 28-day treatment period. In Thailand, NaP can only be found in the form of solution. Previously, this form has not been used for the treatment of chronic constipation. Therefore, we lacked data concerning the dosage. This is a preliminary report of a study aiming to define dose of NaP solution in patient with chronic constipation.

PATIENTS AND METHODS

Inclusion and Exclusion criteria

Ambulatory patients aged between 18 and 60 years were eligible for screening when they had an established diagnosis of functional constipation according to ROME III criteria. The patients who aged over 50 years should perform colonoscopy or flexible sigmoidoscopy and barium enema within the preceeding 10 years were enrolled in this study.

Exclusion criteria were (1) patients with alarm features such as weight loss, anemia, hematochezia (2) history of epilepsy and cardiac disease (3) serum creatinine > 2 mg/dl or calculated creatinine clearance <50 ml/min (4) pregnancy and lactating (5) disability patients (6) patients who were restricted sodium (7) patients with intestinal obstruction, perforation or megacolon (8) use of diuretics, angiotensin converting enzyme inhibitor or angiotensin receptor blocker (9) prolongation of QT interval (10) history of a serious or severe adverse event with previous use of NaP or allergy to any component of NaP solution (11) history use of NaP within 14 days and (12) other disease that in the investigator's opinion would expose the patient to an increased risk for a significant adverse event. Written, informed consent was obtained from all subjects before initiation of the study.

The protocol has been approved by the Ethical Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University.

Study medication

Enrolled subjects were randomly assigned to treatment with NaP solution 10 or 20 cc. The study drug was provided in the exact volume each day. Each 5 ml of NaP solution contains monobasic NaP 2.4 g and biphasic NaP 0.9 g in stable, buffered aqueous solution. During a 28-day treatment period, they were instructed about taking the medication regularly with the option of mixing it with a glass of water.

Study protocol

After the patients were clarified about the procedure during the study, the information about bowel movements were interviewed including frequency, stool consistency and associated symptoms (straining, incomplete defecation, anorectal blockage and digital evacuation). Stool consistency was rated using the Bristol Stool Form Scale (Figure 1). About associated symptoms, a score ranging from 0 (absence) to 3 (severe) was used. Global sensation of symptom score was evaluated by using visual analog scale, ranging from 0 (no change) to 10 (excellent). Postural vital signs, body weight and height were recorded. Serum creatinine, electrolyte, total calcium, phosphorus and electrocardiogram were assessed. Urine pregnancy test was checked in sexually active women.

After the screening, the patients received NaP solution 10 or 20 cc. by randomization. They were

Figure 1. Bristol Stool Form scale

advised to record the frequency and character of their bowel movement by using diary card. Uses of concomitant laxatives and other medications were recorded. Patients were instructed to maintain their usual diet.

Bisacodyl 2 tablets or fleet enema were used as rescue drugs in the patients who had no bowel movement more than 3 days. If bowel movements were more than 3 times per day or Bristol stool form scale 6-7, the patients were recommended to reduce the dose by half.

Patients were encouraged not to use other laxatives during the treatment period. We advised the sexually active women to use a medically acceptable method of birth control.

Patients were assessed weekly. At each visit, patients were asked about compliance and adverse events. The patients returned the completed diary cards. Postural vital signs and body weight were assessed. Serum creatinine, electrolyte, total calcium, phosphorus were analyzed. Treatment was last for 4 weeks.

Study end point

The primary endpoint, "Treatment success" was defined as number of patient with an increase ≥1 bowel movement per 7-day period. These criteria were derived from a report of Talley *et al*[4], in which this was the sole criteria for a constipation response.

Secondary endpoints included (1) number of patient who had an increase in stool consistency at least 1 point of Bristol Stool Form scale and no watery stool (2) number of patient with a decrease at least 1 point of symptom score in straining, incomplete defecation, anorectal blockage and digital evacuation (3) global sensation of symptom score compared with baseline. Information on adverse events was elicited without script at each visit. Severity of adverse events was assessed by investigator according to common terminology criteria for adverse events v3.0 (CTCAE).

Statistical analysis

Continuous data was shown by mean and SD. Binary data was expressed by frequency and percent. About primary outcome which is the binary data was demonstrated by percent with 95% confidential interval.

RESULTS

Seventeen patients were enrolled (16 female and 1 male). Eight patients were assigned to receive 10 cc. NaP solutions (group 1) and 9 patients to receive 20 cc. NaP solutions (group 2). Mean age is 41 ± 8.2 years in group 1 and 41 ± 6.8 years in group 2. Mean of bowel movement is 1.05 ± 0.67 per week in group 1 and 1.04 ± 0.63 per week in group 2.

In group 1, "Treatment success" was found in 50% to 71% as shown in Table1. All patients could complete the study until 4 weeks. During the study period, the number of patient who improved stool consistency was ranging from 50% to 75%. No patient developed watery stool. Symptom score of straining, incomplete defecation, anorectal blockage and digital evacuation in 4 weeks period were improved 63-88%, 71-100%, 29-67% and 33-67%, respectively. Global sensation of symptom score was improved 31-38% from baseline. In group 2, "Treatment success" was 100% (95%CI 70%, 100%) at week 1 as shown in Table1 but 8 of 9 patients had loose to watery stool (Bristol Stool Form scale 6-7). Seven patients developed loose to watery stool at week 1 and 1 patient at week 3. So, only one patient could continue the medication until 4 weeks. At week 1, symptom score of straining, incomplete defecation, anorectal blockage and digital evacuation were improved 33%, 43%, 80% and 33%, respectively. Global sensation of symptom score was improved 20-35% from baseline.

Post-hoc analysis found that number of patient who increase ≥1 bowel movement and no watery stool were 50-71% in group 1 (in 4 weeks period) and 22% in group 2 (evaluate only at first week) as shown in Table 2.

No patient had serious adverse event. One patient in group 2 discontinued the study at week 1 due

Table 1. Number of patient that increase ≥1 bowel movement per 7-day period

Week	Group 1 (n = 8)	Group 2 (n = 9)
1	5/8 (62.5%)	9/9 (100%)
2	5/8 (62.5%)	2/2 (100%)
3	5/7 (71%)	2/2 (100%)
4	4/8 (50%)	0/1 (0%)

Table 2. Number of patient that increase ≥1 bowel movement and no watery stool per 7-day period

Week	Group 1 (n = 8)	Group 2 (n = 9)
1	5/8 (62.5%)	2/9 (22%)
2	5/8 (62.5%)	2/2 (100%)
3	5/7 (71%)	1/2 (50%)
4	4/8 (50%)	0/1 (0%)

to incomplete defecation. One patient in group 2 developed mild hypokalemia (K 3.3 mEq/L), after reduced dose to 10 cc. she developed slightly hypokalemia (K 3.4 mEq/L) again at week 3. Another patient developed slight hypocalcemia at week 2 and week 3 at the level of 7.6 and 7.7 mEq/L (normal 8.4-9.6 mEq/L), respectively. Neither treatment group had postural hypotension, renal insufficiency nor hypophosphatemia.

DISCUSSION

In this preliminary report, daily low dose of NaP solution was effective to increase bowel movement. The efficiency or effectiveness was ranging from 50-71.4% in dose 10 cc. and 100% in dose 20 cc. Although, NaP 20 cc. was more effective but nearly all patients had watery stool. For further study about its efficacy, we suggest to start at dose 10 cc. and escalate dose when there is no increase in bowel movement.

During administration of NaP solution, no patient developed serious adverse events. Only 2 cases developed mild hypokalemia and hypocalcemia. In the previous study taking NaP tablets for 4 weeks, changes in serum concentrations of potassium, calcium and phosphorus were not clinically significant.[3] Now, we do not know about the effect of NaP usage longer than 28 days. Larger sample size and longer duration to monitor the adverse events is needed.

Serious adverse events of NaP solution were reported in elderly patients, who had impaired renal function, dehydration or electrolyte disturbances. Patients in this study were limited to those who had normal renal function and electrolyte. So, we advised them to check renal function, volume status and electrolyte before starting NaP solution. Because of small sample size, we can't recommend the appropriate schedule of checking creatinine and electrolyte during taking NaP solution.

Limitation of this study includes not only its open-label design and lack of placebo or active control group, but also a very small sample size.

In summary, although NaP solution 20 cc. was more effective than 10 cc. to increase bowel movement, nearly all patients developed watery stool. In addition, both dosages seem to be safe for treatment of chronic constipation during the period of 28 days. So, we suggest that using dose 10 cc. for further study is more effective than a standard treatment. No serious side effect was detected in our patients, but we need larger sample size to monitor them. NaP may be the alternative treatment in patient with chronic constipation.

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